

## Supplementary tables

**Supplementary Table S1.** Cancer primary site and their corresponding ICD-O site codes.

| Cancer     | ICD-O   |
|------------|---|
| Bladder    | C67.0, C67.1, C67.2, C67.3, C67.4, C67.5, C67.6, C67.7, C67.8, C67.9                      |
| Breast     | C50.0, C50.1, C50.2, C50.3, C50.4, C50.5, C50.6, C50.7, C50.8, C50.9                      |
| Colorectal | C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C26.0, C19.9, C20.9 |
| Kidney     | C64.9, C65.9  |
| Lung       | C34.0, C34.1, C34.2, C34.3, C34.4, C34.5, C34.6, C34.7, C34.8, C34.9                      |
| Melanoma   | C44.0, C44.1, C44.2, C44.3, C44.4, C44.5, C44.6, C44.7, C44.8, C44.9                      |
| Prostate   | C61.9   |
| Thyroid    | C73.9   |
| Uterine    | C54.0, C54.1, C54.2, C54.3, C54.4, C54.5, C54.6, C54.7, C54.8, C54.9, C55.9               |

**Supplementary Table S2.** Characteristics for the cancer patients.

| Cancer          | Cohort              | Case sample size | Diagnosis age <sup>#</sup> | Female ratio | BMI <sup>*</sup> | Alive | Deceased |
|-----------------|---------------------|------------------|----------------------------|--------------|------------------|-------|----------|
| Bladder         | Phase 1             | 322              | 67.27 +/- 11.83            | 18.32%       | 29.72 +/- 6.01   | 215   | 107      |
|                 | Phase 2             | 93               | 65.72 +/- 12.65            | 25.81%       | 30.76 +/- 6.13   | 86    | 7        |
|                 | TCGA                | 284              | 68.48 +/- 9.90             | 24.65%       | 27.91 +/- 5.56   | 154   | 130      |
| Breast          | Phase 1             | 1214             | 59.37 +/- 11.91            | 100%         | 31.08 +/- 7.20   | 1036  | 178      |
|                 | Phase 2             | 472              | 56.37 +/- 12.16            | 100%         | 30.86 +/- 6.94   | 454   | 18       |
|                 | TCGA                | 735              | 58.60 +/- 13.01            | 100%         | -                | 627   | 108      |
| Colorectal      | Phase 1             | 477              | 64.37 +/- 12.29            | 46.54%       | 30.85 +/- 6.81   | 317   | 160      |
|                 | Phase 2             | 163              | 59.42 +/- 12.74            | 44.79%       | 31.36 +/- 7.22   | 144   | 19       |
|                 | TCGA                | 236              | 64.78 +/- 12.56            | 44.92%       | 27.74 +/- 5.80   | 185   | 51       |
| Kidney          | Phase 1             | 309              | 62.19 +/- 11.53            | 37.22%       | 32.64 +/- 7.40   | 244   | 65       |
|                 | Phase 2             | 94               | 60.27 +/- 11.43            | 39.36%       | 32.73 +/- 6.53   | 86    | 8        |
|                 | TCGA                | 153              | 62.39 +/- 11.80            | 22.22%       | 28.74 +/- 5.34   | 130   | 23       |
| Lung            | Phase 1             | 512              | 67.47 +/- 10.52            | 43.36%       | 28.82 +/- 6.61   | 175   | 336      |
|                 | Phase 2             | 146              | 63.51 +/- 10.19            | 53.42%       | 29.1 +/- 7.11    | 92    | 53       |
|                 | TCGA                | 741              | 66.44 +/- 9.44             | 41.97%       | -                | 448   | 293      |
| Melanoma        | Phase 1             | 730              | 61.32 +/- 14.8             | 42.05%       | 30.42 +/- 6.27   | 614   | 116      |
|                 | Phase 2             | 252              | 57.22 +/- 15.19            | 45.63%       | 30.31 +/- 6.6    | 243   | 9        |
|                 | TCGA                | 439              | 58.12 +/- 15.94            | 37.36%       | -                | 228   | 206      |
| Prostate        | Phase 1             | 1146             | 65.24 +/- 8.05             | 0%           | 30.01 +/- 5.25   | 935   | 211      |
|                 | Phase 2             | 369              | 63.86 +/- 8.74             | 0%           | 30.16 +/- 5.36   | 356   | 13       |
|                 | TCGA                | 147              | 61.09 +/- 6.76             | 0%           | -                | 146   | 1        |
| Thyroid         | Phase 1             | 441              | 48.64 +/- 14.65            | 79.82%       | 31.79 +/- 7.69   | 414   | 26       |
|                 | Phase 2             | 101              | 46.08 +/- 16.14            | 80.20%       | 31.62 +/- 7.88   | 101   | 0        |
|                 | TCGA                | 327              | 47.45 +/- 16.23            | 74.01%       | -                | 314   | 13       |
| Uterine         | Phase 1             | 387              | 60.26 +/- 11.69            | 100%         | 38.33 +/- 9.82   | 342   | 45       |
|                 | Phase 2             | 221              | 61.07 +/- 10.41            | 100%         | 36.76 +/- 10.44  | 209   | 12       |
|                 | TCGA                | 413              | 65.09 +/- 10.84            | 100%         | -                | 319   | 94       |
| Combined cases  | Phase 1             | 5538             | 61.85 +/- 12.71            | 51.97%       | 31.12 +/- 7.18   | 4292  | 1244     |
|                 | Phase 2             | 1911             | 59.38 +/- 12.77            | 57.61%       | 31.37 +/- 7.45   | 1771  | 139      |
|                 | TCGA                | 4004             | 61.41 +/- 13.57            | 56.69%       | -                | 2929  | 1070     |
| Control phase 1 | Common <sup>§</sup> | 7286             | 61.75 +/- 13.54            | 52.46%       | 30.84 +/- 7.09   | -     | -        |
|                 | Female <sup>%</sup> | 7286             | 59.99 +/- 11.99            | 100%         | 32.41 +/- 7.58   | -     | -        |
|                 | Male <sup>^</sup>   | 7286             | 65.43 +/- 8.66             | 0%           | 30.24 +/- 5.30   | -     | -        |
| Control phase 2 | common <sup>§</sup> | 2504             | 58.98 +/- 13.43            | 60.06%       | 31.04 +/- 7.22   | -     | -        |
|                 | female <sup>%</sup> | 2504             | 57.37 +/- 11.37            | 100%         | 31.51 +/- 7.30   | -     | -        |
|                 | male <sup>^</sup>   | 2504             | 63.14 +/- 8.55             | 0%           | 30.19 +/- 5.24   | -     | -        |

Table shows case distribution and characteristics from Phase 1 and Phase 2.

<sup>#</sup>Average Age of patients at diagnosis in years +/- standard deviation

<sup>\*</sup>Average BMI of the patients in kg/m<sup>2</sup> +/- standard deviation

- Missing BMI data. BMI is only available for bladder, colorectal and kidney cancer in TCGA. Missing vital status data for controls.

<sup>§</sup> Common controls were used with bladder, colorectal, lung, kidney, melanoma and thyroid cancer.

<sup>%</sup> Female only controls were used with breast and uterine cancer.

<sup>^</sup> Male only controls were used with prostate cancer.

**Supplementary Table S3.** Total number of variants binned in each cancer type.

| Cancer     | Pathogenic or likely pathogenic |         |        |
|------------|---------------------------------|---------|--------|
|            | Phase 1                         | Phase 2 | TCGA   |
| Bladder    | 76,722                          | 37,518  | 20,382 |
| Breast     | 81,740                          | 41,645  | 21,432 |
| Colorectal | 77,627                          | 38,274  | 20,432 |
| Kidney     | 76,880                          | 37,518  | 21,068 |
| Lung       | 78,222                          | 37,928  | 21,352 |
| Melanoma   | 79,168                          | 38,890  | 20,627 |
| Prostate   | 82,399                          | 39,166  | 19,749 |
| Thyroid    | 77,546                          | 37,735  | 20,471 |
| Uterine    | 76,147                          | 39,324  | 20,723 |

**Supplementary Table S8.** Pathways significantly associated with more than one cancer.

| KEGG Pathway                                | N<br>Cancers | Cancers                              |
|---|--------------|--------------------------------------|
| FoxO signaling pathway                      | 4            | Bladder, Colorectal, Kidney, Lung    |
| GnRH signaling pathway                      | 4            | Bladder, Colorectal, Kidney, Uterine |
| Apoptosis                                   | 3            | Colorectal, Kidney, Lung             |
| Bladder cancer                              | 3            | Bladder, Kidney, Uterine             |
| Axon guidance                               | 2            | Colorectal, Lung                     |
| Basal cell carcinoma                        | 2            | Bladder, Kidney                      |
| Choline metabolism in cancer                | 2            | Kidney, Lung                         |
| Gap junction                                | 2            | Colorectal, Uterine                  |
| Glycerolipid metabolism                     | 2            | Kidney, Melanoma                     |
| Homologous recombination                    | 2            | Breast, Lung                         |
| HTLV-I infection                            | 2            | Bladder, Kidney                      |
| Legionellosis                               | 2            | Bladder, Kidney                      |
| Melanoma                                    | 2            | Kidney, Uterine                      |
| Neurotrophin signaling pathway              | 2            | Colorectal, Melanoma                 |
| Pancreatic secretion                        | 2            | Thyroid, Uterine                     |
| Platinum drug resistance                    | 2            | Kidney, Lung                         |
| Protein processing in endoplasmic reticulum | 2            | Kidney, Uterine                      |
| Rap1 signaling pathway                      | 2            | Lung, Uterine                        |
| Regulation of actin cytoskeleton            | 2            | Colorectal, Lung                     |
| VEGF signaling pathway                      | 2            | Colorectal, Lung                     |

**Supplementary Table S9.** Total number of genes pathogenic and likely pathogenic rare loci were binned in each cancer type.

| Cancer     | Pathogenic or likely pathogenic |                        |                     |
|------------|---------------------------------|------------------------|---------------------|
|            | No. of genes in phase 1         | No. of gene in phase 2 | No. of gene in TCGA |
| Bladder    | 17,246                          | 14,368                 | 10,215              |
| Breast     | 17,428                          | 14,932                 | 10,455              |
| Colorectal | 17,280                          | 14,456                 | 10,219              |
| Kidney     | 17,239                          | 14,378                 | 10,373              |
| Lung       | 17,310                          | 14,436                 | 10,482              |
| Melanoma   | 17,329                          | 14,575                 | 10,247              |
| Prostate   | 17,432                          | 14,641                 | 10,007              |
| Thyroid    | 17,236                          | 14,398                 | 10,235              |
| Uterine    | 17,182                          | 14,629                 | 10,260              |

**Supplementary Table S11.** Genes significantly associated with more than one cancer.

| Cancer     | Gene information |                        | Discovery |          |             |                |                              |
|------------|------------------|------------------------|-----------|----------|-------------|----------------|------------------------------|
|            | Gene             | Chr: Build 38 position | N locus   | MAC Case | MAC Control | SKAT-O p-value | Bonferroni corrected p-value |
| Bladder    | <i>MAPK12</i>    | 22: 50252901-50261810  | 7         | 6        | 42          | 1.18E-06       | 3.74E-03                     |
| Colorectal | <i>MAPK12</i>    | 22: 50252901-50261810  | 9         | 8        | 42          | 1.18E-05       | 3.80E-02                     |
| Colorectal | <i>ECE2</i>      | 3: 184276011-184293031 | 17        | 4        | 17          | 7.23E-06       | 2.33E-02                     |
| Melanoma   | <i>ECE2</i>      | 3: 184276011-184293031 | 20        | 6        | 17          | 2.93E-06       | 9.69E-03                     |
| Lung       | <i>DNMT3A</i>    | 2: 25232961-25342590   | 30        | 10       | 28          | 6.62E-10       | 2.15E-06                     |
| Bladder    | <i>DNMT3A</i>    | 2: 25232961-25342590   | 25        | 6        | 27          | 2.21E-06       | 7.01E-03                     |
| Colorectal | <i>CHIA</i>      | 1: 111290852-111320566 | 9         | 9        | 70          | 4.14E-10       | 1.33E-06                     |
| Melanoma   | <i>CHIA</i>      | 1: 111290852-111320566 | 9         | 8        | 70          | 1.38E-05       | 4.56E-02                     |

**Supplementary Table S13.** Total number of pathway and gene bins used in survival analysis

| Cancer     | Pathogenic or likely pathogenic |                |
|------------|---------------------------------|----------------|
|            | No. of genes                    | No. of pathway |
| Bladder    | 70                              | 276            |
| Breast     | 966                             | 305            |
| Colorectal | 197                             | 286            |
| Kidney     | 51                              | 272            |
| Lung       | 251                             | 293            |
| Melanoma   | 429                             | 300            |
| Prostate   | 986                             | 306            |
| Thyroid    | 170                             | 283            |
| Uterine    | 99                              | 275            |